BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/111,911	07/08/98	WOLD W	16153-5587

HM12/0410

DONALD R HOLLAND
HOWELL AND HAFERKAMP LC
7733 FORSYTH
SUITE 1400
ST LOUIS MO 63105

EXAMINER	
SHUKLA, R	
ART UNIT	**PAPER NUMBER**
1632	13

DATE MAILED: 04/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/111,911	Applicant(s) WOLD, WILLIAM S. M.	
	Examiner Ram Shukla	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,3,4,6,7,10,12-14,17,19,20 and 23-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3,4,6,7,10,12-14,17,19,20 and 23-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 10 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Shukla, whereas any inquiries relating to formal matters should be directed to Ms. Pinkney, Patent Analyst. The phone numbers for Examiner Shukla and Patent Analyst Pinkney are provided at the end of this office action.

2. Claims 2, 5, 8, 9, 11, 15, 16, 18, 21, and 22 have been canceled.

3. Amendments to claims 1, 3, 6, 7, 10, 12, 17, 19, 23, and 24 have been entered.

4. Claims 1, 3, 4, 6, 7, 10, 12-14, 17, 19, 20, and 23-25 are pending.

Specification

5. The disclosure is objected to because of the following informalities: The specification is missing figures 6, 9,11,12, 24 and 25.

Appropriate correction is required. However, applicants are warned that incorporation of new figures may be considered a new matter.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3, 4, 6, 7, 10, 12-14, 17, 19, 20, and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) a composition of a vector wherein said vector comprises a promoter operably linked to a polynucleotide that encodes a RIDα polypeptide disclosed in SEQ ID NO:1 and SEQ ID NO: 2 or a RIDβ polypeptide disclosed in SEQ ID NO:4 and wherein cotransfection of the vectors encoding RIDα and RIDβ polypeptides results in the formation of a Receptor Internalization and Degradation (RID) complex in the cell; (ii) an adenovirus vector wherein the adenovirus vector is 231-10 vector containing a polynucleotide encoding said RID polypeptides; and (iii) an in vitro method of inhibiting apoptosis of a cell, wherein the cell expresses Fas, TNFR-1,DR-3, TRAIL-R1, or TRAIL-2, comprising, administration of the vector(s) to a cell, wherein said cell is used for promoting survival of tumors in mice or for increasing the survival of tumor cells or apoptosing

cells in culture, does not reasonably provide enablement for the claimed methods by providing any and all cells any and all polynucleotides that encode any and all RID polypeptides by any and all routes of administration and treatment of any and all diseases/disorders treated by inhibiting or decreasing apoptosis in any and all patient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention of claims 1, 3, 4, and 6 encompass a method for inhibiting apoptosis of a cell (wherein the cell expresses Fas, TNFR-1, DR-3, TRAIL-R1 or TRAIL-R2) in vivo or in vitro by treating the cell with a polynucleotide or an adenoviral vector that encode any and all RID complexes (wherein the RID polypeptides may be of any length or any sequence, any RID sequence variants), wherein the complex is expressed in the cell in an amount sufficient to inhibit apoptosis of the cell. Claim 6 limits the cell to a leukocyte. Claims 10 and 12-14 recite that the cell is present in a patient. Claims 17, 19 and 20 recite a method of decreasing leukocyte apoptosis. Claim 23 recites a pharmaceutical composition comprising the polynucleotide encoding the RID complex, whereas claim 24 recites a recombinant adenoviral vector encoding RID complex. It is noted that the explicitly intended use for the claimed methods is for treatment of diseases, such as for cancer therapy, autoimmune disease, immunodeficiency diseases, and tissue transplant rejections and implicitly intended use could be for promoting survival of tumors in mice or for increasing the survival of tumor cells or apoptosing cells in culture. However, the specification does not provide sufficient guidance, working example, and disclosure for an artisan to have made and used the claimed invention commensurate with the scope of the claims, without undue experimentation.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discloses a *rec700* mutant adenovirus E1B and E3 proteins and 231-10 vector for the delivery of a polynucleotide encoding the RID complex to several cell lines as examples which illustrate the RID complex efficiency to inhibit/down-regulate apoptosis by Fas-mediated apoptosis pathways and TNFR1(Example 17-35). The specification further disclose the removal or degradation of Fas and TNFR1 from the cell surface by *rec700* (pages 24-30). The specification also demonstrated RID inhibits killing of Ad-infected cells by natural killer cells and cytotoxic lymphocytes. Example 9, discloses 231-10 vector prevents rejection of human cancer cell transplantation into immunocompetent mice. Specification also teaches MT2 based vectors that express RIDα and RIDβ polypeptides.

First, the specification is not enabling for the claimed method wherein a cell is treated with a recombinant polynucleotide encoding RID because given broadest interpretation, claim 1 is interpreted as a method of treating a cell with a cDNA encoding RID polypeptide, however, a cDNA when contacted/treated with a cell may not enter a cell in the first place or even if enters the cell when administered with a carrier such as liposome, it may not express the protein because such would require the presence of a promoter in operable linkage with the cDNA. Furthermore, even when the cDNA is operably linked to a promoter, activity of the promoter would depend on the target cell because promoters may require specific transcription factors for their activity and therefore, may not be active in any and all cells. Therefore, a polynucleotide encoding a polypeptide will be inoperative and for activity will require to be comprised in a vector wherein it is operably linked to a promoter. Next, even if the RID encoding polynucleotide was comprised in a vector, such as an adenovirus vector in claims 3, 12, and 19, the vector may not be able produce sufficient amount of polypeptide to form the complex that would be sufficient to inhibit apoptosis in vivo because the in vitro conditions and examples disclosed in the specification may not be extrapolated to in vivo conditions. It is noted that for practicing the claimed methods in vivo, the most important step is delivery of the vector

exclusively to target cells. Additionally, when the invention is interpreted in the context of in vivo, an artisan would have had to administer the polynucleotide of the invention to a particular cell in a particular tissue (targeted delivery). Again, without a promoter and other regulatory sequences the polynucleotide would not be expressed in a cell.

The art of targeting expression of a polynucleotide to a particular cell or tissue is unpredictable. Eck & Wilson (The Pharmacological Basis of Therapeutics, 1996) teach numerous factors complicate the gene delivery art, which would not have been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein□s compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used and the protein being produced. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al (FASEB J. 9:190-199, 1995) discussed the state of the art of targeted vectors for gene therapy and noted that there is requirement to produce vector systems that can deliver therapeutic genes to the appropriate target cells in vivo or ex vivo and that that these systems should be efficient and accurate. They further stressed that the range of different diseases means that no single delivery system is likely to be universally acceptable and that the stringency with which the therapeutic genes need to be accurately delivered could greatly vary, for example, a vector system used for gene delivery in cystic fibrosis tissue would not be suitable for cancer gene therapy (see first paragraph in column 1 on page 190). Likewise, Deonarain (Deonarain MP. Exp. Opin. Ther. Patents. 8:53-69, 1998) also noted that gene delivery remains the major technological stumbling block in gene therapy strategies. Deonarain further noted that there are several drawbacks of different targeting vectors, such as, risk of secondary malignancies due to integrated vectors, recombination of disabled viruses to produce infective virus, lack of cell specificity, lack of infection of non-dividing cells by retrovirus, inactivation and inactivation of the viral vectors by host complement (see column 1 continued in column 2 on page 54).

In the instant case, an artisan would have to target the expression of the RID complex encoding polynucleotides to a cell, for example, in a transplanted tissue that has been primed to be apoptosed due to immune reaction and not to any other cell of the transplant, and the specification does not teach as to how a RID complex encoding polynucleotide will be targeted to a specific cell of a transplant. It is noted that while the specification teaches inhibition of apoptosis in cell lines (see working examples), all the cells used in the working examples are transformed cells and cancer cells that would have lost the normal mechanisms of cell growth and differentiation, and therefore, as discussed by Miller et al, the experiments disclosed in the specification can not be extrapolated to a tissue in vivo or a primary cell isolated from a tissue and to be used for transplantation or transfusion because the nature of the a primary cell and a transformed cell varies greatly. It is emphasized that the intended uses for the claimed methods are for treatment of autoimmune diseases, degenerative disease, immunodeficiency diseases and tissue transplant rejections (see page 5, lines 2-8), however, the specification does not teach as to how the particular cells that would be affected in these diseases would have been targeted. The specification does not provide sufficient guidance, working examples, and disclosure as to how an artisan of skill would have addressed the problems faced in in vivo targeted delivery of the polynucleotide that encoded a RID polypeptide to a target cell without affecting other cells and an artisan would have had to carry out extensive experimentation to make and use the claimed method and such would have been considered undue, in view of the unpredictability of targeting a polynucleotide to a particular cell in vivo, such that the polypeptide is expressed in amounts sufficient to inhibit apoptosis.

The specification is not enabling for the claimed methods wherein the method is intended for treatment of a disease because the specification does not provide sufficient guidance as to whether an artisan of skill would have been able to treat any and all diseases disclosed in the specification. First the specification does not teach as to how an artisan of skill would have had targeted only those cells of a patients that were undergoing apoptosis and whose retention in the patient would have treated a disease. For example, an artisan would not have known how to target only those cells of the tissue, that were being targeted for apoptosis due to rejection of the transplant, and not those that may be apoptosis due to some other reason, such as a viral infection and their retention may not be desirable. Likewise, it is not clear as to what would be the effect of expressing the RID complex in a leukocyte if a leukocyte was not a target of apoptosis by death receptor mechanism. For example, one of the intended

uses of the claimed methods is to isolate leukocytes of a patient and transduce them with RID encoding polynucleotides and transfuse the cells back in the patient (claims 6 and the method of claims 17 and 19). It is noted that a leukocyte is a general term used to describe immune cells, which include, lymphocytes, phagocytes, and auxiliary cells. Each of these further consist of different cells, e.g. lymphocytes are made up of B and T cells and granular lymphocytes, whereas phagocytes consist of neutrophils, eosinophils and mononuclear phagocytes and auxiliary cells are made up of basophils, mast cells, and platelets. Therefore, when practicing claimed methods, an artisan would be expressing RID complex in all these cells and putting these cells back in a patient and therefore, as asserted by the specification, these cells will not undergo apoptosis when signaled by tumors in the patient. However, this would indicate that these cells would also not undergo apoptosis in response to an infection and therefore, this would be like shutting down the immune system of the patient. It is not clear from the specification as how the leukocytes expressing RID complex would have not apoptosed in response to tumor cell signal but would have undergone apoptosis in response to a viral infection. It is noted that apoptosis is an essential physiological phenomenon required for the maintenance of the normal physiology of an organism and the specification does not provide any guidance as to how an artisan of skill would have differentiated in targeting the expression of RID in only those cells whose retention is essential for normal physiology (see last paragraph in column 1 on page 39 of Uren et al (Pharmacol. Ther. 72:37-50, 1996). Additionally, Uren et al noted that given the tight control of apoptosis in cells, the usefulness of apoptosis-based treatments in part may be limited by their lack of specificity and therefore, treatments that indiscriminately inhibit apoptosis initially may prevent injury- or infection induced apoptosis, but over the long run, allow the survival of potentially malignant cells (see first paragraph in column 1 on page 45). Uren et al also noted that it is essential to know whether apoptosis is an indirect consequence of some other mechanism or is it a direct cause because inhibiting apoptosis where it is indirect consequence may not restore cell function, for example in Alzheimer's disease where inhibiting apoptosis may not prevent further build up of beta-amyloid plaques (see second paragraph in column 1 on page 45). In other words, it is unpredictable whether inhibition of apoptosis would be a viable treatment method, e.g. in Alzheimer's disease, one of the diseases asserted to be treated by the claimed methods.

The specification (in example 9, pages 30-32) discloses that tumor growth was observed when inhibition of apoptosis has occurred and human A549 cancer cells were not rejected when

administered into immunocompetent mouse but there is no indication of controls in response to mock or non-infected tumor cells with or without the administration of an adenovirus vector encoding RID complex. Furthermore, how does the example of growth of tumors in an immunocompetent mouse correlate to graft retention on the basis of modulation of apoptosis or the correlation between decreased apoptosis in tumor cells relate to decrease apoptosis in leukocytes to an effect on transplant tissue? Furthermore, the mouse model of the instant application is not an art-recognized model of tissue transplant rejection. As such, evidence pertaining to a specific vector, gene, promoter, route of administration, and therapeutic effect must be correlative to what is claimed, and in the instant application, a correlation or nexus cannot be drawn for the reasons discussed above.

Furthermore, as presented instantly, claim 1 will encompass polynucleotides that may encode functional variants of RIDα and RIDβ polypeptides or shorter polypeptides (see specification on page 12 and 13). For example, the specification discloses that RID polypeptides of the invention may be derived from any adenoviral serotype or may be mutants of the RID sequences that have the activity. However, the specification does not provide sufficient guidance as to whether any and all functional variants of RID polypeptides would have inhibited apoptosis. It is noted that the RIDa polypeptide has two subunits (90 and 69 amino acids) wherein one of them lacks a signal/anchor domain, whereas RIDb polypeptide has only one subunit (112 amino acids) (see figure 3 in the specification and figure 2 in Stewart et al.). The specification discloses that in a cell 1:1:1 ratio of the polypeptides is required to make a functional RID complex (see page 12, lines 17-20). As recited, claim 1 would also encompass a complex wherein one RID alpha and one RID beta polypeptide would be present in the complex, however, as disclosed in the specification, such a complex will not be functional because all the three polypeptides are required for the RID complex to be operative. In other words, in the instantly recited form, the invention of claims 1, 3, 4, 6, 7, 10, 12-14, 17, 19, 20, and 23-24 would have been inoperative (as disclosed in the specification).

It is noted that the specification does not teach as to what is the minimum number of amino acids or which amino acids of the RIDα or β could be altered without affecting the biological activity or apoptosis inhibiting activity of the RID polypeptides. It is recognized in the prior art that the function of a protein depends on the sequence of its amino acids in a certain pattern, conformation of the protein due to the amino acid sequence, and the functional properties of the different parts of the protein (see second paragraph in Rudinger J in Peptide

Hormones. Editor Parsons JA. Pages 1-7, 1976, University Park Press, Baltimore). Rudinger further add, "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see conclusion on page 6). The specification does not teach which changes in the amino acid sequence of SEQ ID NO 1, 2, 4 would encode polypeptides that would retain the function of the RID complex. Additionally, it is noted that there are disulfide linkage and domains that span through the membrane or are cytoplasmic or extracellular and there is no disclosure in the specification as to which of these domains could be altered without the formation of the RID complex, which contains 1:1:1 ratio of three polypeptides of the complex because even single amino acid change in the polypeptide sequences may result in change in the folding of the polypeptides or complex formation, as noted by Rudinger et al.

Therefore, the specification does not provide any readily available examples that effectively demonstrate the inhibition of apoptosis for a therapeutic treatment of degenerative disease or an immunodeficiency disease or any disease. The specification fails to correlate the polynucleotide delivery to determining the efficiency of RID polypeptide complex in inhibiting apoptosis. Furthermore, the cited arts clearly indicate an unpredictable status of the gene therapy art. And, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect. As the claims are not limited to any specific embodiment of gene therapy nor shown direct correlative effect to treating a patient suffering from a degenerative disease or immunodeficiency disease, despite the *in vitro* demonstration of infection of the adenovirus encoding RID complex was sufficient to protect tumor cells from being rejected in C57BL/6 and Balb/c mice from the Examples in the specification.

The courts have stated that reasonable correlation must exist between scope of a right to exclude patent application and scope of enablement set forth in patent application. 27USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving treatment of <u>any and all</u> disease/disorder and <u>any and all</u> routes of administration as broadly claimed, the lack of direction or guidance provided by

the specification was well as the absence of working examples with regard to a therapeutic effect treating degenerative disease or immunodeficiency disease by protein therapy, it would have required undue experimentation of one skilled in the art to use the claimed invention as broadly claimed.

In conclusion, the specification does not provide sufficient guidance, working example, and disclosure for an artisan of skill to have practice the claimed invention and an artisan of skill would have required to carry out extensive experimentation address the issue raised above and such experimentation would have been undue and therefore, limiting the scope of the invention to (i) a composition of a vector wherein said vector comprises a promoter operably linked to a polynucleotide that encodes a RIDα or RIDβ polypeptides disclosed in SEQ ID NO:1, SEQ ID NO: 2 and SEQ ID NO:4 and wherein cotransfection of the vectors encoding RIDα and RIDβ polypeptides results in the formation of a Receptor Internalization and Degradation (RID) complex in the cell; (ii) an adenovirus vector wherein the adenovirus vector is 231-10 vector containing a polynucleotide encoding said RID polypeptides and (ii) an in vitro method of inhibiting apoptosis of a cell, wherein the cell expresses Fas, TNFR-1,DR-3, TRAIL-R1, or TRAIL-2, comprising, administration of the vector(s) to a cell, wherein said cell is used for promoting survival of tumors in mice or for increasing the survival of tumor cells or apoptosing cells in culture, is proper.

Response to Arguments

Applicant's arguments filed 1-16-01 have been fully considered but they are not persuasive. It is noted that new grounds of rejections have been made and therefore, response to those arguments would be provided which are pertinent to the instant grounds of rejection.

Applicants have argued that claim 1 is not directed to a treatment of a patient, therefore enablement deficiencies would not apply to this claim. However, these arguments are not persuasive because claim 1 does no limit the method to an in vitro method or that it will not be used for treatment. Therefore, given broadest interpretation, it will still encompass a treatment method. Regarding applicant's arguments that the method of claims 10, 14, and 17 do not require alleviation of disease and only require a decrease in apoptosis. Again these arguments are not persuasive because the intended use of inhibiting apoptosis is for treatment and enablement requires both making and using an invention for the intended use and therefore, treatment will be required to full fill enablement requirements.

Next, applicants have argued that they have provided sufficient teachings and guidance regarding routes of administration in their examples, such as in examples 2-8. In response it is noted that the specification teaches expression of the polynucleotides into transformed cell lines and tumor cells, however, the claimed methods are to be practiced in primary cells that would be present in a patient whether cells are treated with the polynucleotides in vitro or in vivo and as has been discussed above, the results obtained in tumor cells or transformed cells can not be extrapolated to primary cells because tumor cells or transformed cells may have lost cell physiological mechanisms.

Next applicants have argued that the applicants teach a mouse model of transplanting human cancer cells and that these cells are not rejected and grow in to a tumor and based on this an artisan would have understood that the specification is enabling for an in vivo method. Again it is noted that the claimed method is for treating a degenerative, autoimmune, or immunodeficiency disease in a patient, wherein the method is stop cells from apoptosis, not rejection of tumor cells. Therefore, the mouse model presented can not be compared to treatment methods (see discussion in the enablement rejection).

Next the applicants have argued that based on the results of the mouse model, an skilled artisan would have understood that RID complex would have prevented NK- and CTL-mediated apoptosis in transplanted tissue when the tissue was treated in vivo after transplantation and in support, applicants have used a review article on gene therapy of transplantation by Giannoukakis et al. Again, it is reiterated that transplantation of a tumor cell in a mouse can not be compared to a transplantation of a tissue in a patient because the cells being acted on by the immune system in a patient are primary cells and in the example disclosed human 459 cells were transduced with an adenoviral vector expressing RID complex, however, when treating a transplanted tissue the polynucleotide would be targeted into the cells of the tissue and as discussed above, a method of targeted expression of a gene sufficient to effect treatment is highly unpredictable. It is reiterated that applicants arguments that an skilled artisan would understand that based on their results in the mouse model, RID complex would effectively eliminate death receptor is not persuasive because the mouse model of the instant application is not an art recognized model of tissue rejection. In response to applicants discussion of the article by Giannoukakis et al, it is noted that Giannoukakis et al provide a review of: steps at which one could potentially intervene at the molecular level, the possible novel genetic interventions as well as cell therapies, which could promote engraftment and

survival and existing and potential strategies and do not provide guidance as to how an artisan would have practiced a method of treatment of a disease in a patient. As has been discussed in the enablement rejection, although, specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest which results in a therapeutic effect.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 3, 4, 6, 7, 10, 12-14, 17, 19, 20, and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 10, and 17 are vague and indefinite because it is unclear as to what is meant by "treating the cell with a recombinant polynucleotide." The specification does not define as to what is encompassed by treating of a cell with a polynucleotide, such as contacting a cell with the polynucleotide, or transfecting/transducing a cell with the polynucleotide, etc.

Claims 3, 12, and 19 are vague and indefinite because they recite the phrase "the polynucleotide comprises a recombinant adenovirus vector". It is not clear as to, if the polynucleotide was to comprise an adenoviral vector, how could the polynucleotide be expressed in a cell, since the polynucleotide encoding the RID polypeptide has to be cloned in the adenoviral vector for the vector to express the RID polypeptide and not the other way round.

Claims 1, 10, 17, 23, and 24 are vague and indefinite because it is unclear as to how can a polynucleotide encode a complex of polypeptide, wherein the complex is made up of three different polypeptides form a complex due to disulfide bond formation after translation.

Claim 24 is indefinite because it recites "which RID complex is operably linked to a promoter." It is unclear as to how can a polypeptide complex be operably linked to a promoter.

Claim 7 is vague and indefinite because it is unclear as to whether "the cell in a transplant" recited in the claim is before transplantation or after transplantation in a patient.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 3, 23, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Stewart et al (J. of Virology, Vol. 69 (1): 5871-5881), for reasons of record repeated below.

The invention of claims 1 and 3 recite a method for inhibiting apoptosis of a cell (wherein the cell expresses Fas, TNFR-1, DR-3, TRAIL-R1 or TRAIL-R2) by treating the cell with a polynucleotide or an adenoviral vector encodes a RID polypeptide complex wherein the complex is expressed in the cell in an amount sufficient to inhibit apoptosis of the cell. Claim 23 recites a pharmaceutical composition comprising the polynucleotide encoding the RID complex, whereas claim 24 recites a recombinant adenoviral vector encoding RID complex.

Stewart et al teach an adenovirus E3 10.4K and 14.5K proteins (two protein function as a complex), which function to prevent/protect cytolysis by tumor necrosis factor and to down-regulate the epidermal growth factor receptor, are localized into plasma membrane. Stewart et al further teach that both proteins are localized in the plasma membrane and that trafficking of each protein to the plasma membrane depends on concomitant expression of the other protein and that neither protein is secreted (abstract). Stewart et al teach several mutants of the E3 region such as *rec700* and *pm760* to observe the preventive or protective function of the E3 region proteins in human KB cells, A549 and A431 cells (page 173, Material and Methods, column 1). Stewart et al also teach that 10.4K-14.5K complex blocks TNF cytolysis by interfering with the function of one or more of the membrane-associated proteins that participate in TNF signaling (page 180, column 2).

Thus, Stewart et al clearly anticipates the invention of claims 1, 3, 23, and 24.

Response to Arguments

12. Applicant's arguments filed 1-16-01 have been fully considered but they are not persuasive. Applicants have argued that Stewart et al does not treat a cell with RID complex to inhibit apoptosis and that Stewart et al does not suggest a treatment would be successful.

However, these arguments are not persuasive because the claimed method comprises a step of treating a cell with a polynucleotide expressing RID complex wherein the complex is expressed in the cell and results in inhibition of apoptosis of the cell wherein the cell expresses Fas TNFR1, DR3, TRAIL-R1 or TRAIL-R2 and the method of Stewart et al also teaches a method of treating a cell with recombinant adenovirus that inhibit TNFR mediated cell cytolysis and the cell cytolysis or cell death is due to the expression of adenoviral 10.4K-14.5K complex. It is noted that inhibition TNFR mediated cell death is inherent to adenoviral 10.4K-14.5K complex and giving it a new name of RID or apoptosis does not change the inherent property of the adenoviral 10.4K-14.5K complex (see MPEP 2112.02).

Response to Amendment

13. The declaration under 37 CFR 1.132 filed 1-16-01 is sufficient to overcome the 102 rejection of claims 1, 3, 23, and 24 based upon based on Dimitrov et al (Apr. 1997), J. of Virology, Vol. 71 (4): 2830-2837 and Krajcsi et al (Aug. 1996), J. of Virology, Vol. 70 (8): 4904-4913.

14. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instruction, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Karen M. Hauda

KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Ram R. Shukla, Ph.D.